REMARKS

The Office Action dated January 8, 2009, has been carefully reviewed and the following comments are made in response thereto. In view of the amendments and the following remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

Prior to discussing the merits of the rejection and solely to clarify the record, Applicants note that any acquiescence to the Examiner's Amendment was for the sole purpose of advancing prosecution (*i.e.* obtaining the previously allowed claims after final) and without any prejudice or disclaimer. Applicants expressly reserve the right to file one or more divisional application to any of the previously canceled claims.

The Rejection under 35 U.S.C. 103 should be withdrawn

Claims 25, 26, and 28 were rejected under 35 U.S.C. 103(a) as being allegedly obvious over (1) Arenberg *et al.* and (2) Strieter *et al.* in view of (3) Rafii *et al.*, (4) Gupta *et al.*, (5) Volin *et al.* and (6) Doranz *et al.* Applicants respectfully disagree, contrary to the Examiner's allegations, the combination of these references would not lead those of skill in the art to make the claimed invention; accordingly, the pending claims are not obvious.

At the time of the invention, it was known that CXCR4 is the receptor specific for the CXC chemokine SDF-1. It was also well known in the art that CXC chemokines can be classified as either angiogenic or angiostatic depending on the presence of the ELR motif in the N-terminus (*see* Moore *et al.* at abstract (copy attached)). In particular, CXC chemokines having the ELR motif (ELR-positive) are potent angiogenic factors while CXC chemokines lacking the ELR motif (ELR-negative) are potent angiostatic factors (Strieter *et al.* J. Biol. Chem. (1995) (copy attached) at abstract). ELR-positive CXC chemokines (such as *e.g.* IL-8) are tumor-derived proteins that promote tumor growth and metastasis (Moore *et al.* at abstract). Conversely, ELR-negative CXC chemokines are endogenous factors that inhibit tumor growth and metastasis (Moore *et al.* at abstract). At the time of the invention, SDF-1 was known to be an angiostatic ELR-negative CXC chemokine (Moore *et al.* page 54, Table 4). Accordingly, at the time of the invention, and as demonstrated by Arenberg *et al.*, those of skill in the art would have expected that inhibition of an ELR-positive CXC chemokine would be effective in the treatment of cancer. On the other hand, those of skill in the art would not have expected inhibition of an ELR-negative CXC chemokine (*e.g.* through inhibition of its sole receptor CXCR4) to be effective in the treatment of cancer.

Arenberg *et al.* disclose treatment of lung cancer with an antibody against IL-8, an ELR-positive CXC chemokine. However, as mentioned above, at the time of the invention, IL-8, an ELR-positive CXC chemokine, was thought to be a potent angiogenic factor while SDF-1, an ELR-negative CXC chemokine, was thought to be a potent angiostatic factor (*see e.g.* Strieter *et al.* J. Biol. Chem. (1995) (at abstract); Moore *et al.* at abstract, page 54, Table 4). Arenberg *et al.* also acknowledge that CXC chemokines are either angiostatic or angiogenic (*see* page 2800, col. 2). Arenberg *et al.* do not disclose or suggest that an anti-human CXCR4 antibody or an anti-human SDF-1 antibody can be used to treat solid tumors, to a disease pathologically caused by neovascularization or to suppress vascularization. The reference also fails to even mention CXCR4 and SDF-1 or their link to cancer.

Strieter *et al.* studied the functional role of the ELR motif in CXC chemokine-mediated angiogenesis and demonstrated, as discussed in detail above, that the CXC family of chemokines displays disparate angiogenic activity depending on the presence or absence of angiogenic activity depending on the absence or presence of the ELR motif (Strieter *et al.* abstract). Strieter *et al.* hypothesized that angiogenesis associated with NSCLC tumor growth is dependent on members of the CXC family acting as either angiogenic or angiostatic factors (Strieter *et al.* page 755). According to this model, if expression of ELR-positive CXC chemokines is favored over ELR-negative CXC chemokines tumor progression occurs (Strieter *et al.* page 755 to 756 and Figure 1). Thus, under this model, one of skill in the art at the time of the claimed invention would have expected tumor progression to occur if the action of an ELR-negative CXC chemokines are inhibited via *e.g.* inhibition of its receptor. Strieter *et al.* do not disclose or suggest that an anti-human CXCR4 antibody or an anti-human SDF-1 antibody can be used to treat solid tumors, treat a disease pathologically caused by neovascularization or to suppress vascularization. The reference also fails to even mention CXCR4 and SDF-1 or their link to cancer.

As the Examiner acknowledges, none of the primary references cited disclose or suggest treating humans expressing CXCR4 or administering anti-human CXCR4 antibody or an anti-human SDF-1 antibody that inhibits the binding between SDF-1 and CXCR4 (*see* page 4 of the Office Action). None of the primary references discloses or suggest that inhibition the ELR-negative chemokine SDF-1 by inhibition of its receptor CXCR4 can be used to treat solid tumors, to treat a disease pathologically caused by neovascularization or to suppress vascularization. Furthermore, none of the secondary references relied upon by the Examiner cures any of the deficiencies of the primary references. Accordingly, the obviousness rejection should be withdrawn.

None of the secondary references cited (Rafii *et al.*, Gupta *et al.*, Volin *et al.*, Doranz *et al.*) disclose or suggest a link between SDF-1 and its receptor CXCR4, solid tumors, a disease pathologically caused by neovascularization and vascularization. Rafii *et al.* describe the relationship between SDF-1

and migration of $CD34^+KDR^+$. Rafii *et al.* disclose that "[t]hese data *suggest* that $AC133^+CD34^+KDR^+$ endothelial progenitor cells reside in the bone marrow microenvironment and upon stimulation with chemokines such as SDF-1 produced as a result of vascular injury, are recruited to the peripheral circulation and *may* play a role in acceleration of vascular endothelialization process" (Rafii *et al.* p. 2 (emphasis added)). Rafii *et al.* do not disclose or suggest that SDF-1 is associated with cancer or neovascularization. Similarly, Gupta *et al.* only suggest that SDF-1α and CXCR4 may play an important role in the etiology of the endothelial cell during vascular disease, inflammation, and infection. Volin *et al.* discusses chemokine receptor CXCR4 expression in the endothelium. Doranz *et al.* teach a monoclonal antibody that binds CXCR4 at the SDF-1 activation site and inhibits SDF-1 signaling (*see* page 5 of the Office Action).

The combination of the references cited by the Examiner cannot render the pending claims obvious. Arenberg *et al.* teach away from the current invention. Arenberg *et al.* teach that inhibition of the *angiogenic* ELR-positive CXC chemokine IL-8 can be used to treat cancer. At the time of the invention, those of skill in the art would have realized, as discussed above, that SDF-1 lacks the ELR motif and thus would have the opposite effect to IL-8. Specifically, those of skill in the art would have expected SDF-1, being an ELR-negative CXC chemokine, to *inhibit tumor growth* and *metastasis*. Accordingly, those of skill in the art would have expected inhibition of SDF-1 (by *e.g.* inhibition of its receptor CXCR4) to result in an increase in tumor growth and metastasis. Thus, those of skill in the art would have never expected that inhibition of SDF-1's receptor, CXCR4, could be used to treat solid tumors, to treat a disease pathologically caused by neovascularization or to suppress vascularization. Accordingly, the claimed invention is unexpected and contrary to what was known at the time of the invention. Since the Arenberg *et al.* reference and conventional wisdom in the art at the time of the invention teaches away from the claimed invention, the pending claims are clearly not obvious.

Given conventional wisdom in the art at the time of the invention – that ECL-negative chemokines and their receptors are associated with tumor repression, those of skill in the art would not have been motivated to make claimed invention or to combine the references cited by the Examiner. In addition, it is clear that even if one of skill in the art would have combined the disclosure of all of the references, the combination of the references does not disclose or suggest all of the features of the pending claims. Furthermore, the fact that the Examiner is relying on a total of six exhibits to make this rejection suggest that the pending claims are not obvious and that the rejection is mere hindsight reasoning.

Accordingly, Applicants request withdrawal of the rejection under 35 U.S.C. 103.

Conclusion

It is respectfully submitted that all claims are now in condition for allowance, early notice of which would be appreciated. Should the Examiner disagree, Applicants respectfully request a telephonic or in-person interview with the undersigned attorney to discuss any remaining issues and to expedite the eventual allowance of the claims.

If there are any additional fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-0310. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,
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